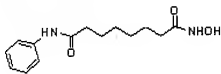


REMARKS

A. Status of the Claims

The application was originally filed with claims 1-6 on November 30, 2003. A Restriction/Election Requirement was mailed on January 18, 2007, requiring election of a single species for prosecution. A Response to Restriction Requirement electing the compound set forth below for use in the treatment of age-related macular degeneration was mailed on February 20, 2007.



All claims were rejected in an Office Action mailed on October 15, 2007. Claim 3 is amended into independent form and to include the compounds from Claim 6. Claim 4 is amended to depend on Claim 3. Claims 1-2 and 5-6 are canceled herein.

B. The Claimed Invention is not Obvious

Claims 1-5 are rejected under 35 USC §103 as being unpatentable over Bressi *et al.* In particular, the Action asserts that one of skill in the art would have been motivated to use the compound shown above to treat macular degeneration and diabetic retinopathy based on the teachings in Bressi *et al.* Applicants respectfully traverse.

The Action alleges that Bressi *et al.* teaches the use of HDAC inhibitors for the treating abnormal angiogenic conditions, including macular degeneration and diabetic retinopathy. The Action further alleges that, based on the teachings in Bressi *et al.*, it would have been obvious to substitute one HDAC inhibitor for another to arrive at the instant invention. However, Applicants respectfully point out that many HDAC inhibitors disclosed in the literature inhibit enzymes that catalyze the acetylation of non-histone proteins, such as transcription factors, cytoskeletal proteins, and chaperones (see for example Di Gennaro *et al.*, *Amino Acids* **2004**, 26(4), 435-441; and Konstantinopoulos *et al.*, *Expert Opinion*

Investigational Drugs 2007, 16(5), 569-571, abstracts of which are attached). The selectivity of the HDAC inhibitors from Bressi *et al.* with respect to enzyme inhibition within (*e.g.*, HDAC-1 vs. HDAC-7 inhibition) and outside of (*e.g.*, acetylation of non-histone proteins) the HDAC family, as well as interaction with other proteins (*e.g.*, ion channels, G-coupled protein receptors, and heat-shock proteins), was not disclosed at the time of the filing of the present application.

Even considering only the HDAC enzyme family, the selectivity of several small-molecule HDAC inhibitors has only recently been disclosed (see for example Khan *et al.*, *Biochemistry Journal* 2008, 409(2), 581-589, abstract attached). Thus, based on the available information at the time the present invention was filed, one skilled in the art could have reasonably concluded that the anti-angiogenic effects alleged for the Bressi compounds might partly be due to interaction with protein targets other than within the HDAC enzyme family, or that the anti-angiogenic effect required a specific inhibition pattern within the HDAC enzyme family (*e.g.*, inhibition of only the HDAC-1 isozyme), with other inhibition patterns (*e.g.*, pan-HDAC inhibition) being ineffective or even detrimental to the anti-angiogenic effect.

Consequently, one skilled in the art would not have been motivated to arrive at the present invention based on Bressi *et al.*, because Bressi *et al.* did not disclose the agents' enzyme and protein interaction selectivity, and because there was a lack of knowledge with respect to whether a specific HDAC enzyme inhibition pattern was required for the alleged ocular anti-angiogenic effects.

Therefore, Applicants submit that the claims are not obvious over Bressi *et al.*, and respectfully request that this ground of rejection be withdrawn.

D. Conclusion

This is submitted to be a complete response to the outstanding Action. Based on the foregoing arguments, the claims are believed to be in condition for allowance; a notice of allowability is therefore respectfully requested.

Serial No.: 10/697,135

The Examiner is invited to contact the undersigned attorney at (817) 615-5330 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

/Jason J. Derry, #50,692/

Jason J. Derry, Ph.D.
Reg. No. 50,692
Attorney for Applicants

ALCON RESEARCH, LTD.
6201 S. Freeway, TB4-8
Fort Worth, TX 76134-2099
(817) 615-5330

Date: January 15, 2008

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1: Amino Acids. 2004 Jul;26(4):435-41. Epub 2004 Jun 11.

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Acetylation of proteins as novel target for antitumor therapy: review article.

Di Gennaro E, Bruzzese F, Caraglia M, Abruzzese A, Budillon A.

Dipartimento di Oncologia Sperimentale, Istituto Nazionale Tumori
Fondazione G. Pascale, Napoli, Italy.

Imbalance in histone acetylation can lead to changes in chromatin structure and transcriptional dysregulation of genes that are involved in the control of proliferation, cell-cycle progression, differentiation and/or apoptosis. Histone acetyltransferases (HATs) and histone deacetylases (HDACs), are two classes of enzymes regulating histone acetylation and whose altered activity has been identified in several cancers. HATs and HDACs enzymes also target non histone protein substrates, including transcription factors, nuclear import factors, cytoskeleton and chaperon proteins. HDAC inhibitors are a novel class of anticancer agents which have been recently shown to induce growth arrest and apoptosis in a variety of human cancer cells by mechanism that cannot be solely attributed to the level of histone acetylation. Several clinical studies with HDAC inhibitors are ongoing, however the molecular basis for their tumour selectivity remains unknown and represent a challenge for the cancer research community.

PMID: 15290351 [PubMed - Indexed for MEDLINE]

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HDAC inhibitors for the treatment of cancer [Curr Opin Investig Drugs. 2003]

Remodeling chromatin and stress resistance in the central nervous system: histone deacetylase inhibitors as novel and broadly effective neuroprotective agents [Curr Opin Neurobiol. 2005]

Histone acetylation and the cell-cycle in cancer. [Front Biosci. 2001]

Protein deacetylases: enzymes with functional diversity as novel therapeutic targets [Cell Cycle Res. 2003]

Histone deacetylase inhibitors in cancer therapy: latest developments, trends and medicinal chemistry perspectives [Mol Cell Biochem. 2007]

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☐ 1: Expert Opin Investig Drugs. 2007 May;16(5):569-71.**Expert Opinion** Full-text article at www.expertin.com Links**Focus on acetylation: the role of histone deacetylase inhibitors in cancer therapy and beyond.****Konstantinopoulos PA, Karamouzis MV, Papavassiliou AG.**

Department of Biological Chemistry, Medical School, University of Athens, 75, M. Asias Street, GR-11527 Goudi-Athens, Greece.

Reversal of tumorigenic epigenetic alterations is an exciting strategy for anticancer drug development. Pharmacologic inhibition of histone deacetylases (HDACs) induces differentiation, proliferation arrest and apoptosis of cancer cells. In addition to their effects on histones, HDAC inhibitors increase the acetylation level of several non-histone proteins, such as transcription factors, cytoskeletal proteins and molecular chaperones, which are crucial in tumorigenesis. Most importantly, the therapeutic potential of HDAC inhibitors goes well beyond carcinogenesis and may include neurodegenerative and inflammatory disorders. This editorial discusses the implication of HDACs in carcinogenesis, the molecular basis of the selectivity of HDAC inhibitors and their possible therapeutic role in non-malignant pathologic conditions.

PMID: 17461732 [PubMed - indexed for MEDLINE]

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Development of histone deacetylase inhibitors for cancer treatment [Expert Opin Investig Drugs. 2007]

Anticancer activities of histone deacetylase inhibitors [Expert Opin Investig Drugs. 2006]

Histone deacetylation in epigenetics: an attractive target for anticancer therapy [Med Res Rev. 2005]

HDAC inhibitors for the treatment of cancer [Expert Opin Investig Drugs. 2003]

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☐ 1: [Biochem J.](#) 2008 Jan 15;409(2):581-9.

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Determination of the class and isoform selectivity of small-molecule histone deacetylase inhibitors.

Khan N, Jeffers M, Kumar S, Hackett C, Boldog F, Khramtsov N, Qian X, Mills E, Berghs SC, Carey N, Finn PW, Collins LS, Tumber A, Ritchie JW, Jensen PB, Lichtenstein HS, Sehested M.

Topotarget UK Ltd, 87a Milton Park, Abingdon, Oxon, OX14 4RY, UK.
nagmabkhan@yahoo.co.uk

The human HDAC (histone deacetylase) family, a well-validated anticancer target, plays a key role in the control of gene expression through regulation of transcription. While HDACs can be subdivided into three main classes, the class I, class II and class III HDACs (sirtuins), it is presently unclear whether inhibiting multiple HDACs using pan-HDAC inhibitors, or targeting specific isoforms that show aberrant levels in tumours, will prove more effective as an anticancer strategy in the clinic. To address the above issues, we have tested a number of clinically relevant HDACis (HDAC inhibitors) against a panel of rhHDAC (recombinant human HDAC) isoforms. Eight rhHDACs were expressed using a baculoviral system, and a Fluor de Lystrade mark (Blomol International) HDAC assay was optimized for each purified isoform. The potency and selectivity of ten HDACs on class I isoforms (rhHDAC1, rhHDAC2, rhHDAC3 and rhHDAC8) and class II HDAC isoforms (rhHDAC4, rhHDAC6, rhHDAC7 and rhHDAC9) was determined. MS-275 was HDAC1-selective, MGCD0103 was HDAC1- and HDAC2-selective, apicidin was HDAC2- and HDAC3-selective and valproic acid was a specific inhibitor of class I HDACs. The hydroxamic acid-derived compounds (trichostatin A, NVP-LAQ824, panobinostat, ITF2357, vorinostat and belinostat) were potent pan-HDAC inhibitors. The growth-inhibitory effect of the HDACis on HeLa cells showed that both pan-HDAC and class-I-specific inhibitors inhibited cell growth. The results also showed that both pan-HDAC and class-I-specific inhibitor treatment resulted in increased acetylation of histones, but only pan-HDAC inhibitor treatment resulted in increased tubulin acetylation, which is in agreement with

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Identification of novel isoform-selective inhibitors within class I histone deacetylases [\[Exp Ther. 2003\]](#)

Class II histone deacetylases are associated with VHL-independent regulation of hypoxia-inducible factor 1 alpha. [\[Cancer Res. 2005\]](#)

Histone deacetylase inhibitors selectively suppress expression of HDAC7. [\[Mol Cancer Ther. 2007\]](#)

Expression and functional characterization of recombinant human HDAC1 and HDAC2. [\[Mol Cell Biochem. 2004\]](#)

Histone acetylation-independent effect of histone deacetylase inhibitors on Akt through the reshuffling of protein phosphatase 1 complexes. [\[J Biol Chem. 2005\]](#)

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their activity towards the HDAC6 isoform.

PMID: 17868033 [PubMed - in process]

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